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ASSOCIATE VICE PRESIDENT
CLINICAL AFFAIRS

PhRMA

2284 '99 SEP 13 P1:30

September 13, 1999

Dockets Management Branch (HFD-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Dear Sir/Madam:

Re: Draft Guidance for Industry: Clinical Development Programs for Drugs, Devices and Biological Products Intended for the Treatment of Osteoarthritis (OA). Federal Register 135, July 15, 1999; Docket # 98D-0077

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, happier, healthier and more productive lives. Investing over 24 billion annually in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

PhRMA appreciates the opportunity to comment on this revised draft Guidance which seeks to guide industry in the development of structure modifying treatments for OA. PhRMA is also pleased to see reference to the relevant European regulatory Points to Consider in the revised draft FDA guidance document. These comments are presented in the order in which information appears in the guidance document.

Section II, Use of Preclinical Models: Paragraph 4, item 3. In evaluating possible usefulness of an animal model, this section calls for consideration of correlating joint structural changes with clinical changes, such as pain, in these animal models. PhRMA considers that correlation of structural changes in animal models with pain/function is not feasible at this time. Animal pain study methods are irrelevant for OA structure/pain questions. Gait analysis is not useful in guinea pigs, and dogs limp after cruciate ligament surgery, but quickly recover co-incident with surgical healing. Furthermore, structural information in animal studies comes from post-mortem histologic examination, and serial

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radiographs have not proven to be useful in preclinical screening of chemical analogs.

Section IV, Osteoarthritis Measurements/ Issue of excessive splitting of claims: Paragraph 1 states

> "Protocols enrolling patients with knee or hip OA (the so-called signal joints) have made measuring and interpreting treatment effects easier, and the development of specific OA measurements has paralleled, and in some ways guided, this signal-joint approach. However, exclusive focus on the signal-joint will miss what is happening at other OA sites. Appropriate measurements, such as using a patient global assessment, or taking a specific non-signal-joint measurement, should be included to capture treatment effects at other OA sites."

PhRMA members have also listened with interest to the questions regarding distribution of evidence from various OA sites that were discussed at the Arthritis Advisory Committee meeting on 21 July 1999. PhRMA agrees that a signal joint can be used in clinical studies and that a global measure is sufficient to follow the non-signal joints. It should be recognized that the metrics for nonsignal joint symptoms and function are still in the early stage of their development. As noted in the Committee discussion, if taken to an extreme, one could theoretically ask for clinical trials in each of the three compartments of the knee; and in the case of the upper extremity, one could assert that DIP (distal interphalangeal) joint OA is different from PIP (proximal interphalangeal) osteoarthritis. This would not make good biological sense, because the pathogenesis of OA is the same in these two examples—when viewed in the appropriate context of weightbearing OA and in the context of hand OA.

PhRMA shares the concerns of members of the Arthritis Advisory Committee regarding excessive splitting of the indication for a structure-modifying drug. PhRMA believes that it is not appropriate to require studies in both hip and knee OA in order to secure an indication for treatment of OA in the weight-bearing joints. The CPMP Points to Consider (July 1998) states that studies showing structural benefit in knee OA will also receive a claim for hip OA, as the pathogenesis of the OA disease is the same in these weight-bearing joints. PhRMA agrees with this requirement, and urges that the FDA adopt this same position and document it in the OA guidance.

Section V.A. Imaging Requirements in Symptom Studies: PhRMA disagrees with requiring imaging studies for signs and symptoms

drugs/therapies. If there are no mechanistic or preclinical data that point toward joint damage, then there is no reason to pursue the matter further in the clinic. Furthermore, symptom modifying studies enroll patients with a much wider range of OA pathology and stages of joint disease than is the case in structure studies where OA disease must be in a carefully defined range in order to make longitudinal observations and still keep sample sizes affordable. Restricting OA study patients excessively would limit the applicability of such symptom studies to the general population.

It is recognized that the WOMAC and Lequesne algofunctional questionaires are well validated for OA research. However, other validated research instruments are also available and should be considered in the context of specific clinical research proposals by sponsors.

Section V.B.3 Slow JSN by at least a pre-specified amount/ Effect size of >50% is too high a hurdle given current state of OA science: PhRMA acknowledges the correction to the draft guidance provided at the 21 July 1999 Arthritis Advisory Committee meeting that "sponsors seeking this claim should anticipate relatively large changes, greater than 50%, in slowing JSN relative to the control arm." PhRMA shares the point of view of members of the Advisory Committee that as the clinically-relevant minimal difference in JSN is yet to be determined, differences of greater than 50% may not be required in order to provide clinical benefit in this patient population. PhRMA agrees that it is not practical to state a minimum absolute value in millimeters for a change in joint space that must be obtained in a study. A percentage change in the progression of JSN compared to placebo is sufficient to show efficacy of drugs that have a joint structure modifying effect.

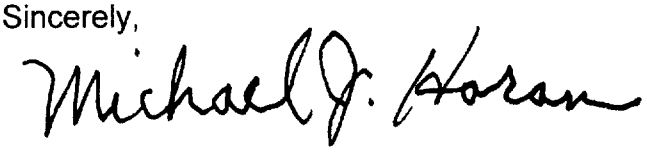
PhRMA supports the Committee's comment that a difference of approximately 30% may be meaningful when using well standardized imaging methods; however, with the current paucity of data in this field, PhRMA proposes that the FDA guidance require simply that a pre-defined difference in JSN be observed, with no deleterious effects on pain and/or function. A reasonable risk-benefit ratio should be demonstrated. Finally, to serve as a guide for initial OA studies with structural endpoints given the limited data available, PhRMA observes that the approach taken in the NIH multicenter doxycycline OA study (which uses a 30% effect size) appears to be a reasonable initial guideline.

Section VI. Trial Designs and Analyses: In addition to reviewing the revised draft guidance, PhRMA members listened with interest to the discussions regarding data analysis at the 21 July 1999 Arthritis Advisory Committee

meeting. From a statistical analysis point of view, PhRMA believes that there is no significant difference between research in OA or other diseases. We therefore propose that adjustments for multiple comparisons with regard to secondary endpoints (eg, pain and function) and handling of missing data should be addressed in accordance with the ICH Guidance on Statistical Principles for Clinical Trials, and that this should not differ between therapeutic areas. The Statistical Guidance indicates that a universally accepted method of handling missing values does not currently exist and that the effect of the missing data for the primary analysis should be investigated. Also the Guidance does not require adjustments for multiplicity due to having secondary variables, but does note that the number of secondary variables should be few and relevant to the scope of the trial. PhRMA is also concerned that through comments concerning adjustments for multiplicity, the revised draft guidance implicitly suggests that studies in OA, with primary emphasis on structure-modification, should be powered for symptom-modifying secondary endpoints. If this were truly the intent, the sample size for phase III studies would be extremely large, posing an unduly burdensome requirement on study sponsors. PhRMA therefore concludes that it is not appropriate for the revised draft OA guidance to contain specific guidance regarding adjustments for multiplicity or methods for handling missing data.

PhRMA appreciates the opportunity to comment on the proposed FDA osteoarthritis guideline and notes the useful improvements that have been made since the first draft of the guidance issued in February 1998. Thank you for consideration of our input, and for incorporating these ideas into the final OA guidance document.

Sincerely,



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